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A computational study to identify potential inhibitors for human chymase from natural and/or biogenic sources

Dubey A(1,2), Marabotti A(1,3), Ramteke PW(2), Facchiano A(1)

(1) CNR-ISA, National Research Council, Institute of Food Science, via Roma 64, Avellino-83100, Italy.
(2) Jacob School of Biotechnology and Bioengineering, Sam Higginbottom Institute of Agriculture, Technology and Sciences, Allahabad- 211007, India.
(3) Department of Chemistry and Biology "Adolfo Zambelli", University of Salerno, Via Giovanni Paolo II 132, Fisciano-84084 (SA), Italy.

Motivation
The human chymase (EC 3.4.21.39) is a hydrolase abundant in secretory granules of mast cells, responsible for the synthesis of angiotensin II from its precursor. Moreover, it is also responsible for the conversion of transforming growth factor-β (TGF-β) and matrix metalloproteinase (MMP)-9 precursors to their active forms. Since a link between heart failure and chymase has been proved, specific chymase inhibitors are actively searched to develop new therapeutic treatments for cardiovascular diseases, considering also that chymase has no enzymatic activity in normal tissues. Therefore, specific chymase inhibitors may have no effects on any other target in healthy states.
The use of natural products has been an integral part of the treatment of different diseases throughout the world since past centuries. Many plants with potential therapeutic activity were widely used as natural medicines with negligible undesired effects. Therefore, the search for new active compounds from natural sources is gaining interest in the scientific community, and the application of novel approaches to an old science could result in the discovery of valuable compounds useful to develop innovative drugs.
We present here our search for novel inhibitors of chymase enzyme from natural sources or inspired by nature, using a computational approach that allowed us to screen databases of compounds and to predict which molecules can be able to bind to chymase with a good affinity and selectivity against other serine proteases.

Methods
The crystal structure of human chymase complexed to a known inhibitor, available in the Protein Data Bank (PDB code 1T31), was selected for the development of ten structure-based pharmacophore models, using the protocol available in Discovery Studio. After a validation step, the best pharmacophore was used to screen a special subset of ZINC database (ZINC Biogenic compounds) containing more than 120,000 nature-inspired compounds. After identification of the best potential compounds matching the pharmacophore features, and further filtering strategies, few potential ZINC compounds were selected for further steps. In parallel, selected compounds from plants were identified as potential candidates, also on the basis of their correspondence to the pharmacophore features obtained in the previous step.
The 3D structures of all these selected compounds, as well as those of the known co-crystallized chymase inhibitor and of other known inhibitors used as reference molecules, were retrieved from ZINC and/or PubChem databases and were docked in the active site of human chymase. Their predicted binding affinities and their

interactions with the enzyme were then compared. Finally, all these molecules were docked into the active sites of other human serine proteases (kallikrein, elastase and tryptase), whose 3D structures were selected in their turn from PDB database, in order to predict their selectivity towards chymase.

Results

Among the few selected compounds obtained from ZINC Biogenic database (1), most are predicted to bind human chymase with a binding energy comparable, or even better, with respect to the one predicted for known inhibitors. Among the compounds selected from plants (2), all show a negative binding energy, suggesting a potential ability to interact with the enzyme, but the absolute values are often higher with respect to those of known inhibitors, indicating a less favorable interaction. The analysis of the complexes with the best predicted energies shows that these molecules can interact with the key residues involved in substrate binding and catalysis. Moreover, several compounds are able to interact with chymase with a good selectivity towards the other tested serine proteases, since the predicted binding energy for these last enzymes is in some cases significantly higher with respect to that for chymase.

In conclusion, the selected molecules can become novel candidates for the therapeutic action in the context of cardiovascular diseases, making them good candidates for further experimental studies to characterize their activity in vitro and in vivo. Our results also shows a possible explanation of their inhibitory mechanism and important structural insights which extent our expertise for drug designing against enzyme targets, enhancing the possibility for the potential development of future drugs.

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